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Synthesis, Characterization of Some New Heterocycles bearing benzofuran Moiety

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ABSTRACT

1-(Benzofuran-2-yl)-3-(substituted phenyl)-prop-2-ene-1-one (1-5) were prepared by the reaction of 2-acetylbenzofuran with different aromatic aldehydes in presence of alkali. Reaction of the prepared chalcones with hydroxylamine, urea, thiourea and phenylthiourea gave 3-(benzofuran-2-yl)isoxazoline derivatives (6-10), 4-(benzofuran-2-yl)pyrimidinone (11-15), 4-(benzofuran-2-yl)pyrimidinethione (16-20) and 4-(benzofuran-2-yl) substituted pyrimidinethione (21-26) successively. The characterization of all synthesized compound was done by IR and for some of the compounds by ¹H and ¹³C-NMR and CHN analysis.

Keywords: 1-(Benzofuran-2-yl)-3-(substituted phenyl)-prop-2-ene-1-one, 3-(benzofuran-2-yl)isoxazoline derivatives, 4-(benzofuran-2-yl)pyrimidinone, 4-(benzofuran-2-yl)pyrimidinethione

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INTRODUCTION

Benzofuran derivatives possess a wide range of biological activities. They have reported to possess antimicrobial [1-4], antitumour [5,6], anti-inflammatory [7] activity since nitrogen containing heterocycles such as isoxazoline, pyrimidine and pyrimidinthione are possessing structural moiety for drug designing as an example pyrimidine based heterocycles are potential bioactive molecules and exhibit antimicrobial [8], anti-inflammatory [9], antioxidant [10] anticancer and also acts as enzyme inhibitors. Inspired from these facts, we have synthesized some benzofuranpyrazolines, benzofuranisoxazoles and benzofuranthiopyrimidinones derivatives starting from chalcones containing benzofuran.

MATERIALS AND METHODS

EXPERIMENTAL

General: The melting points were recorded by electrothermal apparatus and uncorrected. IR spectra were recorded as KBr disc on Shimadzu FT-IR 8400 S Fourier transform-Infrared spectrophotometer. $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ were recorded at Aal AL- Bayt University-Jordan (300 MHz) using DMSO-d_6 as solvent and TMS as internal standard. The elemental analyses were recorded at the same university.

2-Acetylbenzofuran

A mixture of salicylaldehyde (0.1 mol, 12.2 g), chloroacetone (0.1 mol, 9.20 g) and potassium carbonate (30.0 g) was gently heated under reflux in dry acetone (150 mL) for 13 hr. The reaction product, after cooling, was filtered under reduced pressure to give the required product as a dark yellow coloured solid. Recrystallized from ethanol gave the desired material (9.60 g, 60%), mp 68-70°C [mp 70-71°C [11].

1-(Benzofuran-2-yl)-3-(substituted phenyl)prop-2-ene-1-one (1-5) [12]

(2E)-1-(1-Benzofuran-2-yl)-3-[4-(dimethylamino)phenyl]-2-propen-1-one (1): Typical procedure for the synthesis of compounds (1-5):

A mixture of aromatic benzaldehyde (0.01 mol, 1.49 g) and 2-acetylbenzofuran (0.01 mol, 1.60 g) was dissolved in a minimum amount of ethanolic potassium hydroxide solution (25 ml, 0.02 mol, 1.12 g) and the mixture was stirred for 2h until the entire mixture became cloudy, then the mixture was poured slowly into (400 mL) of water with constant stirring and kept in refrigerator for 24 h. The precipitate obtained was filtered, washed and recrystallized from ethanol to give the required product (2.26 g, 78%), mp 118-120°C.

3-(Benzofuran-2-yl)isoxazoline derivatives [13]

The preparation of compound 6, Table (2) was used as a typical procedure for this reaction.

To a mixture of chalcone (0.01 mol, 2.91 g) and hydroxyl amine hydrochloride (0.01 mol, 0.69 g), absolute ethanol (50ml), aqueous sodium hydroxide (10%, 6 mL) was added then the reaction mixture was heated under reflux for 5h and poured slowly into ice cold water and the product obtained was washed with water and recrystallized from ethanol 95%. The required material was obtained (2.14 g, 70%), mp 86-88°C.

Pyrimidinone derivatives (11-15): [13]:

The preparation of compound 11, table 3 was used as a typical example for the reaction.

To a solution of (0.01 mol, 2.91 g) of chalcone, absolute ethanol (50 ml), urea (0.01 mol, 0.6 g) of aqueous sodium hydroxide (10 ml, 0.40 g, 10 mmol) was added. The reaction mixture was heated under reflux for 5h and poured in ice-cold water. The product obtained was filtered washed with water and recrystallized from ethanol (95%) to give the required product (2.01 g, 60%), mp (108-110) °C.

Pyrimidinethion derivatives (16-20) [13]

The preparation of compound (16) Table (4) was used as a typical procedure for this reaction.

To a solution of chalcone (0.02 mol, 5.82 g) absolute ethanol (100 mL), thiourea (0.02 mol, 1.52 g) and aqueous sodium hydroxide (10 mL, 20.0 mmol) were added. The reaction mixture was heated under reflux for 7h and poured into iced cold water the product obtained was filtered, washed with water and recrystallized from ethanol-water (1:1) to give the required product (5.47 g, 78%), mp 117-119°C.

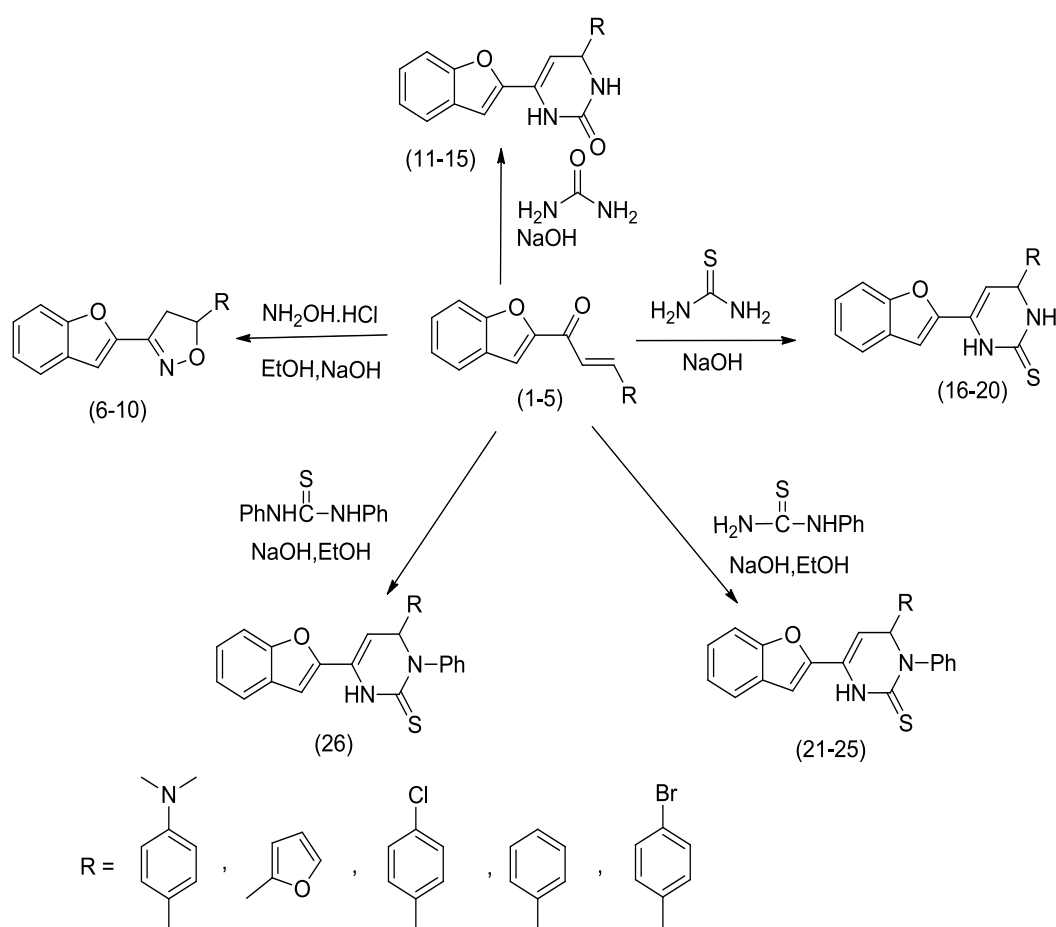
1-Phenyl-6-(benzofuran-2-yl)pyrimidinethione derivatives (21-26) [13]

The preparation of compound (21) Table (5) was used as typical procedure for this reaction.

To a solution of chalcones (0.01 mol, 2.91 g) in absolute ethanol (50 mL), phenylthiourea (1.52 g, 0.01 mol) and aqueous sodium hydroxide (10 mL, 0.01 mol, 0.40 g) were added and the mixture was heated under reflux for 7h and poured into iced cold water and the product obtained was filtered washed with water and recrystallized from ethanol (95%) to give the required product (3.31 g, 77%), mp 167-170°C.

6-(Benzofuran-2-yl)-4-(furan-2-yl)-3-phenyl-3,4-dihydropyrimidine-2(1H)-thione (26):

The title compound was prepared from chalcone (2.92 g, 0.01 mol), diphenylthiourea (2.28 g, 0.01 mol) and aqueous sodium hydroxide (10 mL, 0.4 g, 0.01 mol) in absolute ethanol (50 ml) and the mixture was heated under reflux for 8h then the same procedure was followed as above, (2.68 g, 72%), mp 165-166°C.



Scheme 1: Synthetic route to compounds 6-26

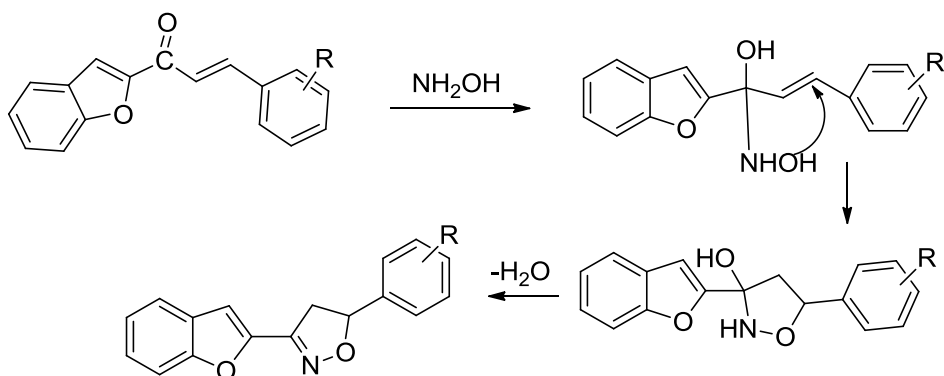
RESULTS AND DISCUSSION

The syntheses of chalcones, isoxazoline, pyrimidinone, pyrimidinthion, and substituted pyrimidinthion derivatives were performed as shown in scheme (1).

Chalcones (1-5) were synthesized by condensing 2-acetylbenzofuran with appropriate aromatic aldehydes in ethanolic potassium hydroxide at room temperature. Compounds (6-10), (11-15), (16-20), (21-26) were synthesized by reacting the appropriate chalcones with hydroxyl amine, urea, thiourea, and substituted thiourea successively. All the compounds were characterized by IR (tables 6 and 7). Also, some of these compounds were characterised by $^1\text{H-NMR}$ (table 8), $^{13}\text{C-NMR}$ (table 9), UV spectra (table 6 and 7) and CHN analysis (table 10).

Condensation of substituted benzofuryl chalcones with hydroxyl amine

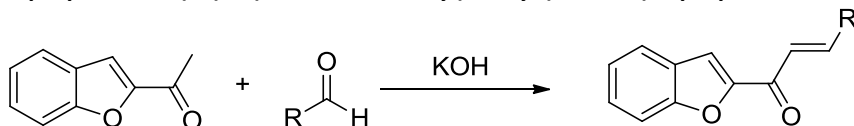
Hydroxylamine hydrochloride was condensed with substituted chalcones to afford substituted 2-isoxazoline. The mechanism of the reaction of benzofurylchalcones with hydroxylamine is shown in scheme (2).



Scheme 2: Reaction mechanism of chalcones with hydroxylamine hydrochloride

Condensation of substituted benzofuryl chalcones with urea and thiourea—Urea, thiourea and substituted thiourea were condensed with substituted benzofuryl chalcones under basic conditions to afford the corresponding pyrimidinone, pyrimidinthione and substituted pyrimidinthione compounds, and the mechanism

of the reaction probably includes the attack of $\text{HN}^{\ominus}\text{C}(=\text{O})\text{NH}_2$ or $\text{HN}^{\ominus}\text{C}(=\text{S})\text{NH}_2$ anion on the double bond of the α,β -unsaturated system by Michael addition [11]. The mechanism for the reaction is illustrated in scheme (3).

Table 1: Physical properties of (2E)-1-(1-benzofuran-2-yl)-3-aryl (or furan)-2-propen-1-one "chalcones" (1-5)


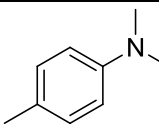

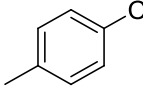
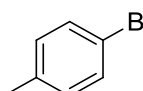
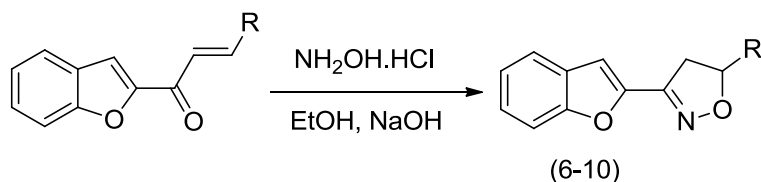
Compound No	Product Name	R	mp °C/(ref):mp	Colour	Yield (%)
1	(2E)-1-(1-benzofuran-2-yl)-3-[4-(dimethylamino)phenyl]-2-propen-1-one		118-120 (14) 138-140	Reddish orange	78
2	(2E)-1-(1-benzofuran-2-yl)-3-(2-furyl)-2-propen-1-one		102-104 (14) 90-92	Brown	75
4	(2E)-1-(1-benzofuran-2-yl)-3-(4-chlorophenyl)-2-propen-1-one		110-112 (14) 130-132	Brown	69
5	(2E)-1-(1-benzofuran-2-yl)-3-(4-bromophenyl)-2-propen-1-one		124-126	Brownish yellow	70

Table 2: Physical properties of 3-(1-benzofuran-2-yl)-5-aryl (or furan)-4,5-dihydroisoxazole (6-10)


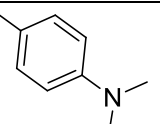

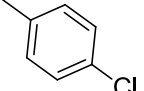

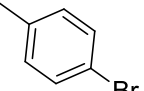
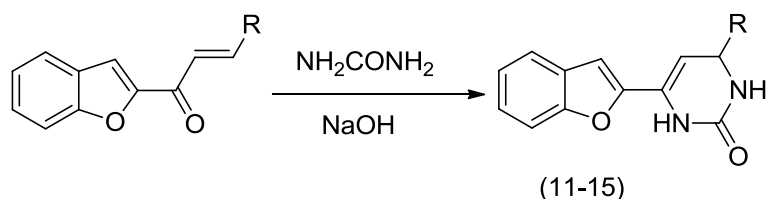
Compound No.	Product Name	R	mp °C	Colour	Yield (%)
6	N-[4-[3-(1-benzofuran-2-yl)-4,5-dihydro-5-isoxazolyl]phenyl]-N,N-dimethylamine		88-86	Dark-brown	70
7	3-(1-benzofuran-2-yl)-5-(2-furyl)-4,5-dihydroisoxazole		141-143	Yellowish brown	65
8	3-(1-benzofuran-2-yl)-5-(4-chlorophenyl)-4,5-dihydroisoxazole		149-151	bright Brown	64
9	3-(1-benzofuran-2-yl)-5-phenyl-4,5-dihydroisoxazole		71-73	Dark-brown	75
10	3-(1-benzofuran-2-yl)-5-(4-bromophenyl)-4,5-dihydroisoxazole		81-83	Yellowish brown	68

Table 3: Physical properties of 6-(1-benzofuran-2-yl)-4-aryl (or furan)-3,4-dihydro-2(1H)-pyrimidinone (11-15)


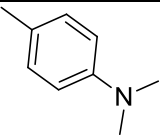

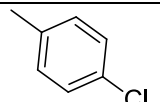

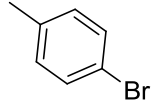
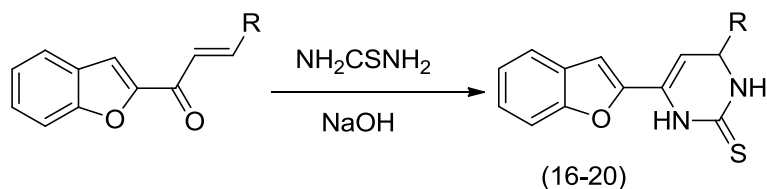
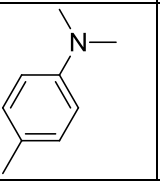

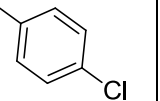

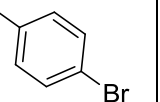
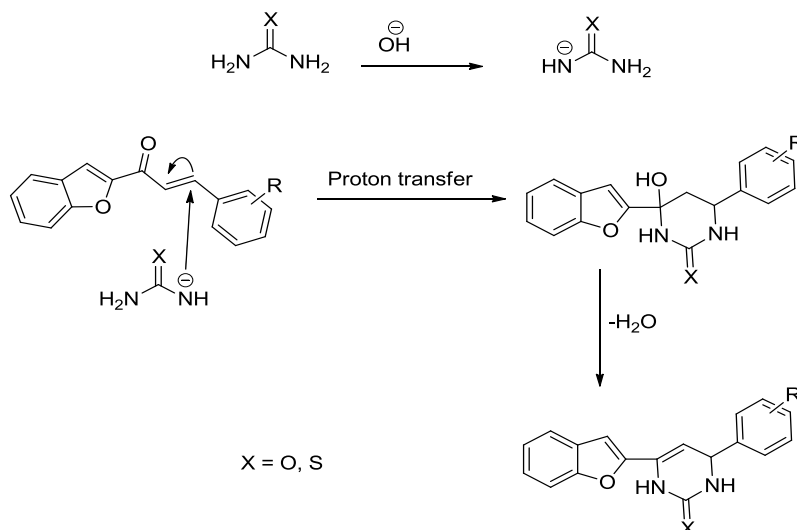
Compound No.	Name of Product	R	mp °C/(ref):mp	Colour	Yield (%)
11	6-(1-benzofuran-2-yl)-4-[4-(dimethylamino)phenyl]-3,4-dihydro-2(1H)-pyrimidinone		108-110	Orange	60
12	6-(1-benzofuran-2-yl)-4-(2-furyl)-3,4-dihydro-2(1H)-pyrimidinone		115-117	Light brown	61
13	6-(1-benzofuran-2-yl)-4-(4-chlorophenyl)-3,4-dihydro-2(1H)-pyrimidinone		185-188 (16) 282	Brown	65
14	6-(1-benzofuran-2-yl)-4-phenyl-3,4-dihydro-2(1H)-pyrimidinone		124-126 (16) 234	Brown	67
15	6-(1-benzofuran-2-yl)-4-(4-bromophenyl)-3,4-dihydro-2(1H)-pyrimidinone		172-175	Yellowish Brown	59

Table 4: Physical properties of 4-(benzofuran-2-yl) substituted Pyrimidinethione (16-20)


Compound No.	Name of Product	R	Mp °C	Colour	Yield (%)
16	6-(1-benzofuran-2-yl)-4-[4-(dimethylamino)phenyl]-3,4-dihydro-2(1H)-pyrimidinethione		117-119	Reddish brown	78
17	6-(1-benzofuran-2-yl)-4-(2-furyl)-3,4-dihydro-2(1H)-pyrimidinethione		158-161	Brown	81
18	6-(1-benzofuran-2-yl)-4-(4-chlorophenyl)-3,4-dihydro-2(1H)-pyrimidinethione		88-91	Brownish yellow	73
19	6-(1-benzofuran-2-yl)-4-phenyl-3,4-dihydro-2(1H)-pyrimidinethione		160-162	Brownish yellow	78
20	6-(1-benzofuran-2-yl)-4-(4-bromophenyl)-3,4-dihydro-2(1H)-pyrimidinethione		Decomposed 230	Yellow	70



Scheme 3: Proposed reaction mechanism of chalcones with urea or thiourea

Table 6: Spectral data of substituted chalcones (1-5)

Compound No.	UV(EtOH) (λ_{max})nm	IR (KBr), $\nu(\text{cm}^{-1})$				
		C=O	C=C	C \equiv C	C-O-C	Others
1	325	1653	1575	1543	1159	
2	338	1658	1598	1553	1139	
3	372	1664	1612	1592	1139	C-Cl 681
4	361	1666	1606	1551	1139	
5	369	1656	1609	1548	1073	C-Br 583

Table 7: UV and IR spectra of compounds (6-26)

Compound No	UV(EtOH) (λ_{max})nm	IR(KBr) $\nu(\text{cm}^{-1})$								
		C=N	C=C	C \equiv C	C=O	C=S	C-O-C	C-O-N	N-H	others
6	292	1659	-	1596	-	-	1099	1306	-	-
7	297	1632	-	1585	-	-	1107	1310	-	-
8	306	1658	-	1599	-	-	1101	1305	-	C-Cl=693
9	308	1658	-	1595	-	-	1082	1351	-	-
10	319	1642	-	1578	-	-	1112	1322	-	-
11	304	-	1599	1557	1663	-	1092	-	3393	-
12	309	-	1598	1556	1664	-	1178	-	3394	-
13	329	-	1600	1557	1666	-	1135	-	3380	C-Cl=695
14	337	-	1604	1562	1672	-	1162	-	3382	-
15	322	-	1611	1550	1663	-	1153	-	3447	C-Br=590
16	308	-	1655	1603	-	1163	1163	-	3419	-
17	292	-	1650	1601	-	1139	1121	-	3425	-
18	325	-	1654	1598	-	1138	1130	-	3392	C-C=654
19	313	-	1664	1595	-	1166	1144	-	3423	-
20	3220	-	1636	1559	-	1148	1137	-	3421	C-Br=580
21	296	-	1596	1546	-	1203	1114	-	3392	-
22	315	-	1598	1549	-	1157	1109	-	3207	-
23	343	-	1600	1565	-	1180	1099	-	3420	C-Cl=691
24	321	-	1606	1548	-	1153	1127	-	3448	-
25	924	-	1611	1550	-	1160	1132	-	3436	C-Br=582
26	251	-	1607	1573	-	1170	1119	-	3428	-

Table 8: ¹H-NMR data δ (ppm) of some of the prepared compounds

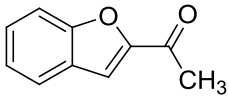
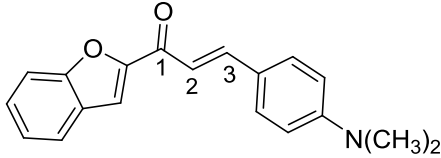
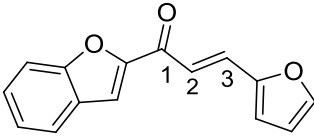
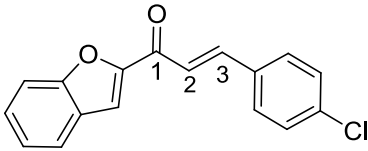
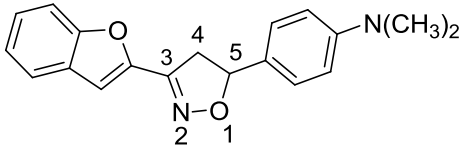
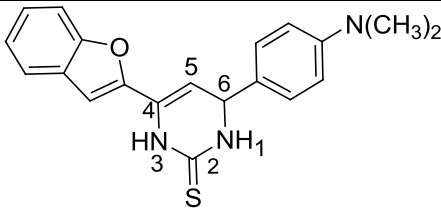
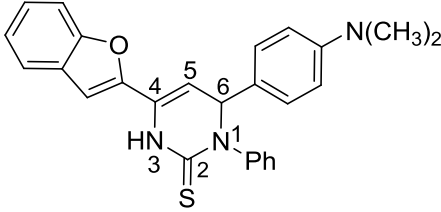
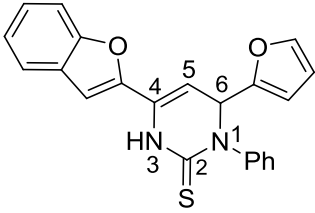
Compound No	Structure	¹ H NMR (DMSO-d ₆)
—		2.56 (3H, s, CH ₃), 7.51 (1H, s, furan), 7.34-7.89 (Ar-H, m, 4H).
1		3.03 (6H, s, N-(CH ₃) ₂), 7.60 (1H, s, furan), 6.76 (1H, d, C-2), 7.54 (1H, d, C-3), 7.05- 7.57 (9H, m, ArH).
2		6.70 (1H, d, C-2), 7.56 (1H, d, C-3) 7.101-7.650 (7H, m, Ar-H), 7.60 (furan ring conjugated with benzene ring).
3		6.63 (1H, d, C-2), 7.23-7.49 (8H, m, Ar-H), 7.56(1H, d, C-3), 7.58(furan ring conjugated with benzene ring).
6		2.87 (6H, s, N-(CH ₃) ₂), 3.94 (2H, d, C-4), 5.73 (1H, t, C-5), 6.52-7.59 (8H, m, Ar-H), 6.70 (furan ring conjugated with benzene ring).
16		2.77 (1H, s, N-H), 2.82 (1H, s, N-H), 2.90 (6H, s, N-(CH ₃) ₂), 5.05 (1H, d, C-6), 6.74 (1H, d, C-5), 6.75 (furan ring conjugated with benzene ring), 6.88-7.66 (8H, m, Ar-H).
21		2.92 (6H, s, N-(CH ₃) ₂), 6.56 (1H, d, C-6), 6.57-7.58 (13H, m, Ar-H), 6.75 (1H, d, C-5), 6.78 (furan ring conjugated with benzene ring), 2.71(1H, s, N-H).
22		1.34 (1H, s, N-H), 4.50(1H, d, C-6), 6.72(1H, d, C-5), 6.73 (furan ring conjugated with benzene ring), 7.15-7.97 (12H, m, Ar-H).

Table 9: ^{13}C -NMR Data of some of the prepared compounds

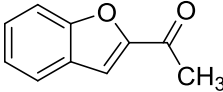
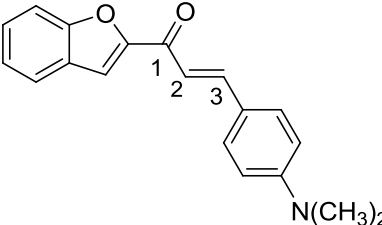
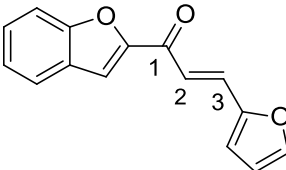
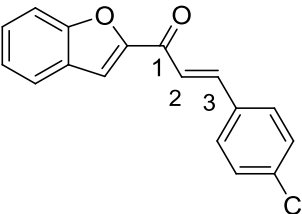
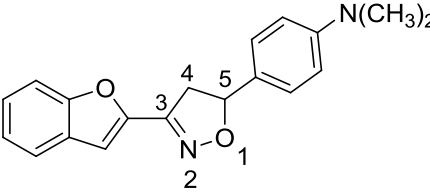
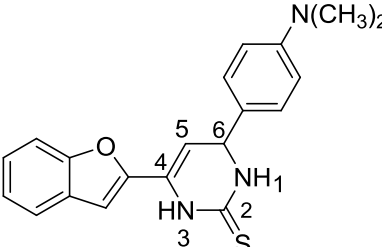
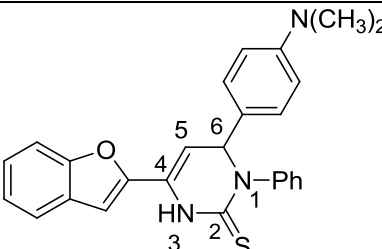
Compound No	Structure	^{13}C NMR (DMSO- d_6)
----		26.9, 112.7, 114.7, 121.0, 124.1, 124.5, 128.0, 875.0, 152.6, 155.4, 188.4
1		40.2, 112.2, 112.7, 113.9, 116.3, 122.1, 123.9, 124.4, 127.6, 128.6, 131.5, 145.2, 152.7, 154.5, 155.5, 178.7
2		112.7, 113.7, 114.8, 118.3, 118.9, 124.1, 124.5, 127.5, 128.9, 130.4, 146.9, 153.6, 178.6
3		112.8, 115.9, 123.0, 124.3, 124.6, 128.47, 128.8, 131.1, 133.8, 135.8, 142.5, 153.6, 155.8, 178.8.
6		41.4, 42.8, 73.4, 106.1, 111.6, 114.6, 121.0, 123.3, 124.1, 128.1, 128.7, 130.5, 146.3, 148.6, 154.8, 155.2
16		40.2, 54.3, 102.8, 104.4, 111.4, 113.9, 122.1, 123.8, 124.5, 127.7, 131.5, 131.6, 148.8, 150.4, 150.6, 154.4, 174.8
21		40.8, 111.5, 112.2, 112.7, 114.7, 116.3, 122.1, 123.9, 124.4, 127.2, 127.6, 128.6, 128.8, 129.3, 131.5, 145.2, 154.4, 152.4, 155.5, 178.7

Table 10: Elemental analysis of compounds: 2, 3, 16 and 26.

Compound No	Molecular formula	Elemental microanalysis (%)(Calculated/Found)			
		C (%)	H (%)	N (%)	S (%)
2	C ₁₅ H ₁₀ O ₃	77.27	4.03	—	—
		77.58	4.31	—	—
3	C ₁₇ H ₁₁ O ₂ Cl	71.88	4.31	—	—
		72.21	3.89	—	—
16	C ₂₀ H ₁₉ ON ₃ S	68.21	4.93	11.84	9.62
		68.76	5.44	12.03	9.16
26	C ₂₈ H ₂₀ N ₂ O ₂ S	75.70	5.08	6.12	7.08
		74.98	4.46	6.24	7.16

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